8e Initial
Contains No CBI

NA Industries, Inc.
New York Office (Nippon Shokubai)
101 East 52nd Street
New York, NY 10022
Phone (212) 759-7890 Fax (212) 838-5258

NIPPON SHOKUBAI

93 OCT -1 PM 2:27

8EHQ-0993-1272

A

September 27, 1993

Document Processing Center
Office of Toxic Substances
Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Att: (8e) Coordinator

Re: Styrene/N-phenyl maleimide copolymer

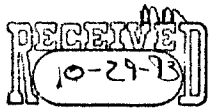
Dear Sir/Madam:

NA Industries, Inc., a subsidiary of Nippon Shokubai Co., Ltd. submits the following document:

1. Styrene/N-phenyl Maleimide Co-polymer Micronised and Non-micronised, Acute Inhalation Toxicity in Rats 4-hour Exposure.

The documents contain information which may reasonably support the conclusion that the referenced chemical may present a substantial risk of injury to human health or the environment, as indicated in the Reporting Guide provided by EPA. The information is summarized below:

1. The rats exposed to syrene/N-phenyl maleimide co-polymer showed exaggerated respiratory movements and test material on fur and tail.
2. Reduced bodyweight or a reduced rate of bodyweight gain was observed in the rats exposed to the test material.
3. Food and water consumption of the rats exposed to the test material was reduced.
4. The lung weight to bodyweight ratio of some rats exposed to the test material was higher than that of the control rats.
5. An increase in the incidence of minimal pneumonitis, minimal increased numbers of alveolar macrophage and minimal perivascular lymphoid infiltration in lungs of the female rats was observed.



83 pgs.

6. Alveolar macraphage containing globular inclusions were detected among the rats exposed to the test material. The LC_{50}(4-hour) for the test material is in excess of 2.11 mg/1 of air.

NA Industries, Inc., requests guidance from EPA whether the Agency believes the information contained in this document satisfies the Section 8(e) reporting criteria.

If you have any questions or comments, please do not hesitate to call me at (212)759-7890.

Sincerely yours,

NA INDUSTRIES, INC.

Hidetaka Yatagai, Ph.D.
General Manager

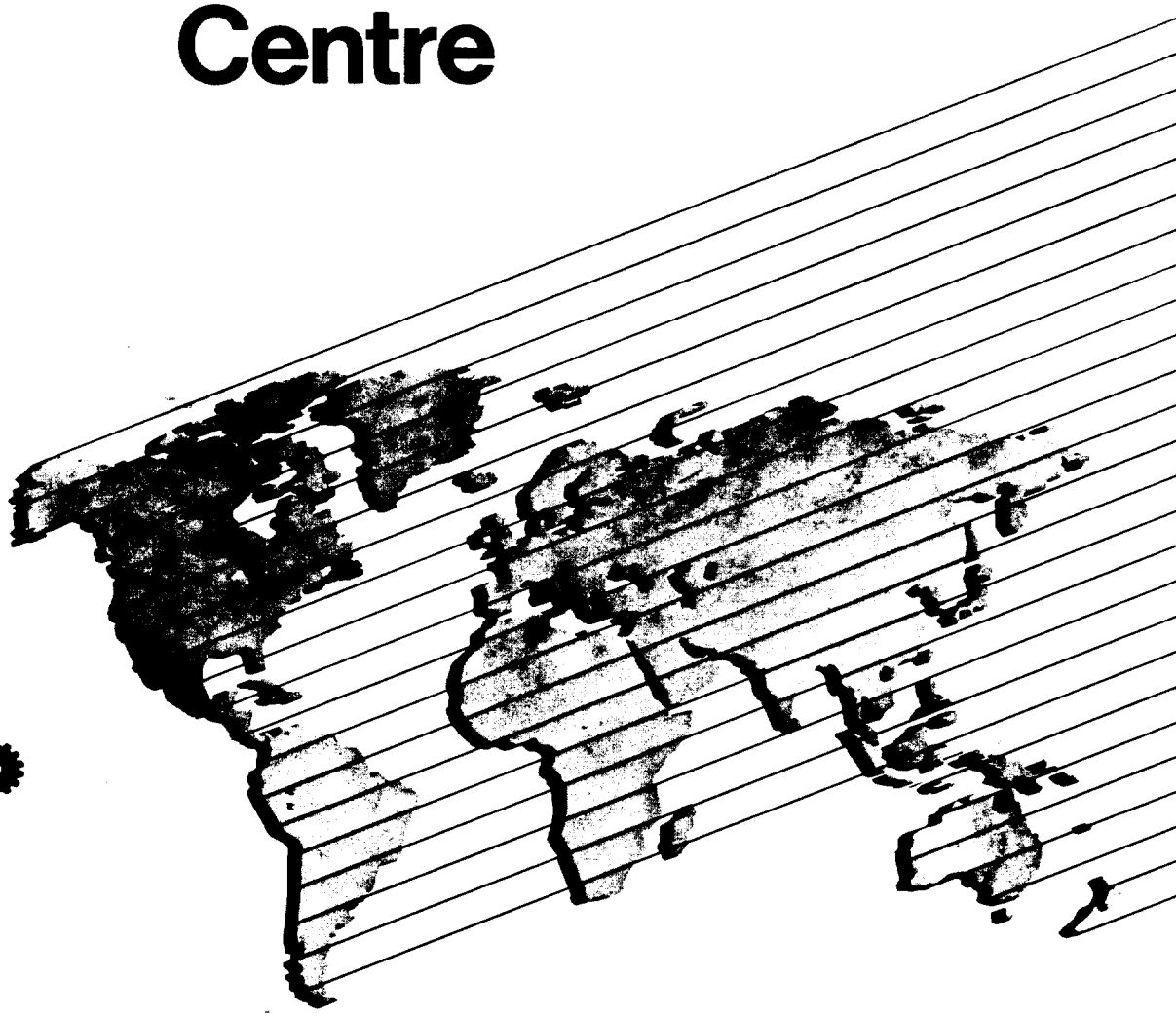
HY/jmc

HRC Report

STYRENE/N-PHENYL MALEIMIDE
CO-POLYMER MICRONISED AND
NON-MICRONISED

ACUTE INHALATION TOXICITY
IN RATS 4-HOUR EXPOSURE

Huntingdon Research Centre



1989

STYRENE/N-PHENYL MALEIMIDE CO-POLYMER MICRONISED AND NON-MICRONISED

ACUTE INHALATION TOXICITY IN RATS 4-HOUR EXPOSURE

Study completed: 16 July 1993

Regulations: EPA TSCA 798.1150

Addressee:

Dr. K. Fujioka,
Nippon Shokubai Company Limited,
Himeji Research Laboratory,
992-1, Nishioki, Okihama,
Aboshi-ku, Himeji-shi,
Hyogo-ken 671-12,
JAPAN.

Testing facility:

Huntingdon Research Centre Ltd.,
P.O. Box 2,
Huntingdon,
Cambridgeshire,
PE18 6ES,
ENGLAND.

Report issued 16 July 1993

CONFIDENTIALITY STATEMENT

This report contains the unpublished results of research sponsored by Nippon Shokubai Co. Ltd. These results may not be published, either wholly or in part, or reviewed or quoted in any other publication without the prior authorisation of the Sponsor.

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The Study described in this Report was conducted in compliance with the following Good Laboratory Practice Standards and I consider the data generated to be valid.

Good Laboratory Practice, The United Kingdom Compliance Programme, Department of Health & Social Security 1986 and subsequent revision, Department of Health, 1989.

United States Environmental Protection Agency, (TSCA), Title 40 Code of Federal Regulations Part 792, Federal Register, 29 November 1983 and subsequent amendment Federal Register 17 August 1989.

Japanese Ministry of International Trade and Industry, Directive 31 March 1984 (Kanpogyo No. 39 Environmental Agency, Kikyoku No. 85 MITI).

Organisation for Economic Co-operation and Development, ISBN 92-64-12367-9, Paris 1982.

G. C. Jackson

Graham C. Jackson, B.A. (Hons.), L.R.S.C.,
Study Director,
Huntingdon Research Centre Ltd.

16 July 1993

Date

RESPONSIBLE PERSONNEL

We the undersigned, hereby declare that the work was performed under our supervision according to the procedures herein described, and that this report provides a correct and faithful record of the results obtained.

G. C. Jackson

Graham C. Jackson, B.A. (Hons.), L.R.S.C.,
Study Director,
Department of Inhalation Toxicology.

Graeme K. Molloy, B.Sc. (Hons.),
Study Supervisor,
Department of Inhalation Toxicology.

C. J. Hardy

Colin J. Hardy, B.Sc., Ph.D., M.I.Biol., C.Biol., Dip.R.C.Path. (Toxicology),
Senior Toxicologist,
Division of Toxicology.

H Singh

Harcharn Singh, B.V.Sc. & A.H., D.T.V.M., M.Sc., M.R.C.V.S.,
Pathologist,
Department of Pathology.

John M. Offer, B.Sc., Ph.D., M.I.Biol.,
Consultant Pathologist,
Department of Pathology.

Gopinath

Chirukandath Gopinath, B.V.Sc., M.V.Sc., Ph.D., F.R.C.Path.,
Director of Pathology.

QUALITY ASSURANCE STATEMENT

Certain studies such as that described in this report, are conducted at HRC in a setting which involves frequent repetition of similar or identical procedures. At or about the time the study described in this report was in progress, 'process-based' inspections were made by the Quality Assurance Department of critical procedures relevant to this study type. For the inspection of any given procedure, at least one study was selected without bias. The findings of these inspections were reported promptly to the Study Director and to HRC Management.

This report has been audited by the Quality Assurance Department. It is considered to be an accurate description of the procedures and practices employed during the course of the study and an accurate presentation of the findings.

Date of inspection	7 - 8 May 92 3, 4 and 6 November 92
Date of reporting inspection findings to the Study Director and HRC Management	8 May 92 6 November 92
Date of reporting audit findings to the Study Director and HRC Management	22 June 93

G.R. Keeble — 15 July 1993

G.R. Keeble,
Systems Compliance Auditor,
Department of Quality Assurance,
Huntingdon Research Centre Ltd.

CONTENTS

RESULTS

FIGURES

TABLES

APPENDICES

SUMMARY

Test substance:	A white powder identified as Styrene/N-phenyl maleimide co-polymer, non-micronised and micronised.
Test animals:	Albino rats, (Sprague-Dawley). Two control groups and 2 test groups each of 5 male and 5 female rats.
Route of administration:	By inhalation of a test atmosphere containing a particulate aerosol generated from the test substance, in micronised or non-micronised form.
Duration of exposure:	4 hours continuous whole-body exposure.
Observation period:	14 days post exposure.

Results

Exposure levels of Styrene/N-phenyl maleimide co-polymer:	1.33 mg/l of air. This was the highest attainable concentration for the non-micronised test substance. For the micronised test substance, the highest attainable concentration was 2.11 mg/l.
Mortality:	There were no deaths.
Clinical signs:	(a) During exposure: In both micronised and non-micronised exposures, the rats were not visible due to the test atmospheres. (b) During observation period: Generally signs seen in rats exposed to Styrene/N-phenyl maleimide co-polymer included, exaggerated respiratory movements and test material on fur and tail. All rats exposed to Styrene/N-phenyl maleimide co-polymer were normal by Day 2 of the observation period.

Bodyweight:

Reduced bodyweight or a reduced rate of bodyweight gain was observed for 1 day following exposure. Subsequently weight gain was similar to that for control rats.

Food and water consumption:

Food consumption was reduced for 1 day following exposure to Styrene/N-phenyl maleimide co-polymer.

Water consumption for exposed rats was generally reduced for up to 1 day, subsequently consumption was similar to that of control rats.

Lung weight to bodyweight ratio:

The lung weight to bodyweight ratio for 2 female rats exposed to the non-micronised sample (1.33 mg/l of air) was higher than that of the control rats. Also, one male rat exposed to the micronised sample (2.11 mg/l) had a higher lung weight to bodyweight ratio than control rats.

Macroscopic pathology:

Dark spots were found on the lungs of 6/10 control rats and 7/10 test rats exposed at 1.33 mg/l of air (non-micronised). There were no abnormalities in rats exposed at 2.11 mg/l (micronised)

Microscopic pathology:

The following treatment-related changes were observed in rats exposed at 1.33 mg/l (non-micronised):

Lungs

An apparent increase in the incidence of minimal pneumonitis, minimal increased numbers of alveolar macrophages and minimal perivascular lymphoid infiltration in lungs of the female rats compared to controls.

Treatment-related changes in rats exposed at 2.11 mg/l (micronised) were:

Lungs

Alveolar macrophages containing globular inclusions were detected in 9/10 rats from the treated group. In one of these male rats, these macrophages were aggregates around terminal bronchioles.

CONCLUSION

The LC_{50} (4-hour) for Styrene/N-phenyl maleimide co-polymer is in excess of 2.11 mg/l of air. The concentration of Styrene/N-phenyl maleimide co-polymer in air was the highest attainable using the procedures described.

INTRODUCTION

The acute inhalation toxicity of Styrene/N-phenyl maleimide co-polymer was assessed by exposing 2 groups of rats to a test atmosphere containing the maximum attainable concentration of aerosol that could be produced from the test substance as received (non-micronised) or from the micronised test substance. Two additional groups acting as controls were exposed to clean air only for 4 hours.

The studies were conducted at the Huntingdon Research Centre during the periods 7 May to 29 May 1992 and 28 October to 18 November 1992.

The protocols for the studies were approved by the Study Director and HRC Management on 10 February and 8 July 1992 and approved by the Sponsor on 10 March and 22 July 1992 respectively.

The study design was in compliance with the following test guidelines for acute inhalation studies:

EPA TSCA:	798.1150
OECD:	Method 403
EEC:	Method B2

On completion of the studies all data relating to the studies, including preserved tissues and a copy of the final report, were lodged in the Huntingdon Research Centre Archives, Huntingdon, Cambridgeshire, England.

MATERIALS AND METHODS

Test substance

The test substance was a white powder identified as:

Styrene/N-phenyl maleimide co-polymer
Batch no.: P-1 Y 23 (PSR-9)

The test substance was used as received and in a micronised form.

The sample was received on 16 March 1992 and was stored at room temperature in the original container. Under these storage conditions the sample was stable for at least 2 years.

Approximately 1 kg of the test substance was air-milled by Micron Mills Ltd., St. Pauls Cray, Orpington, Kent, to reduce the particle size to the extent technically possible.

The test substance is referred to as Styrene/N-phenyl maleimide co-polymer (micronised or non-micronised) in this report.

Animals and maintenance

Study with non-micronised test substance

Ten male and 10 female albino rats (Sprague-Dawley), about 6 weeks and 8 weeks old respectively, were selected from a single consignment of rats obtained from Harlan Olac Limited, Shaw's Farm, Blackthorn, Bicester, Oxon., OX6 0TP, England on 7 May 1992.

Study with micronised test substance

Ten male and 10 female albino rats (Sprague-Dawley), about 6 weeks and 8 weeks old respectively, were selected from a single consignment of rats obtained from Charles River UK Limited, Manston Road, Margate, Kent, England on 28 October 1992.

The rats were selected so that males and females would be of similar bodyweight (*ca.* 200 g) on the day of exposure.

On arrival the rats were allocated to 1 of 2 groups, each of 5 males and 5 females and were identified individually by a number tattooed on the ears. The rats were housed 5 of like sex to a cage and acclimatised to laboratory conditions for at least 5 days before the day of exposure.

The holding cages (size 35 cm x 53 cm x 25 cm height) were made of stainless steel sheet and wire mesh and were suspended on a movable rack. While in their cages all rats had free access to a measured excess amount of food (SDS RM1) and tap water. Food and water supplies were analysed routinely to determine the levels of chemical or microbiological contaminants.

The rats remained in a holding room except for the 4-hour exposure and an overnight post exposure period when the rats in the test group were kept in a ventilated cabinet to allow dispersal of any residual test substance.

The holding room was illuminated by artificial light between 8 a.m. and 8 p.m. daily.

The temperature and relative humidity of the holding room air was recorded continuously using a Kent Clearspan recorder.

The temperature of the holding area during the study remained within the limits of 18°C and 25°C and the relative humidity was between the limits of 25% and 65%.

There were no extremes of temperature or relative humidity considered likely to influence the results of the study.

Inhalation exposures

A group of rats was exposed continuously for 4 hours to a test atmosphere containing a particulate aerosol generated from Styrene/N-phenyl maleimide co-polymer as received, and a second group received the test substance in air-milled (micronised) form.

Two further groups acting as controls received clean air only for 4 hours.

The group identifications and dates of exposure for the groups were:

Non-micronised		Micronised	
Group 1A (Control)	15 May 1992	Group 1B (Control)	4 November 1992
Group 2A (Test)	15 May 1992	Group 2B (Test)	4 November 1992

The mean concentrations of Styrene/N-phenyl maleimide co-polymer in the test atmosphere are given in the 'Results' section of this report.

Exposure system

Wright dust generator

A Wright dust generator ([1]) was used to produce the test atmospheres containing the dust of Styrene/N-phenyl maleimide co-polymer as received and in micronised form.

The design of the generator is shown in Figure 1. The generator was designed to produce and maintain test atmospheres containing dust by suspending material scraped from the surface of a compressed powder in a stream of dry air. The concentration of dust in the air may be altered by changing the rate at which the scraper blade is advanced into the compressed powder. The maximum concentration of dust attainable is dependent on the particle size of the test substance and the density and physical properties of the compressed powder.

([1]) Wright, B.M., J.Scient. Instruments, **27** (1) 1950, p 12

Aerosol conditioning

The test aerosol for Group 2A was passed through a glass elutriation column to reduce, by sedimentation, the amount of non-respirable particulate in the test atmosphere. For Group 2B the test atmosphere was passed through an aerosol neutraliser (Thermo Systems, Inc., Model 3054) to reduce electrostatic charge effects and also to function as an elutriator.

Exposure chambers

The whole-body exposure chambers used for the exposures were of square section and were fitted with pyramidal tops. The chambers were made of perspex and had an internal volume of approximately 120 litres. Each chamber was divided by wire mesh partitions to provide 10 separate animal compartments.

The test atmosphere entered through a port at the base centre of the chamber and passed out through small holes in the lower edge of the square section. Each chamber was positioned inside a large cabinet equipped with an extract fan exhausting to atmosphere through a collection filter.

The exposure system in the configuration used for Group 2B is shown in Figure 2. The configuration for Group 2A was similar except that a glass elutriation column was used instead of the aerosol neutraliser (B).

Procedure

The samples of Styrene/N-phenyl maleimide co-polymer were packed into the container of the Wright dust generator using a hydraulic bench press to assist packing. Even density of the powder was achieved by packing the container in stages and applying a force of 0.2 tons weight for the non-micronised sample and 0.4 tons weight for the micronised sample. The packed container was weighed.

The dust generator was positioned on a stand at the side of the exposure chamber and the output connected to an inlet port in the top centre of the chamber through the elutriation column or through the aerosol neutraliser. The speed controller of the generator mechanism was set to give the required concentration of dust (1).

A supply of clean, dried compressed air was connected to the dust generator and the supply pressure was adjusted to give a flow rate of 25 litres per minute measured at the generator outlet nozzle. The total chamber air supply was derived from the air flow through the dust generator.

For each exposure the rats (5♂ and 5♀) were placed into separate compartments of the exposure chamber.

(1) The performance of the dust generator was assessed during a preliminary trial. A setting of 80% of the maximum speed was found to be the highest for reliable operation of the dust generator

The powder container of the Wright dust generator was advanced manually until a trace of suspended dust was seen in the chamber. The gearing on the generator was then engaged and the generator motor switched on to start the exposure. After an 11-minute (2) equilibration period, the exposure was timed for 4 hours. The generator was then switched off and the chamber allowed to clear before the rats were removed for examination.

Following exposure, the rats were returned to the holding cages and food and water supplies were restored. The test rats were kept in a ventilated cabinet overnight and then returned to the holding room for the remainder of the observation period.

The control groups were treated similarly but exposed to clean air only for 4 hours.

The control rats were returned to the holding room at the end of the exposure procedure.

Chamber atmosphere analyses

Five air samples were taken from the chamber during the exposures and the collected material was weighed to determine the concentration of total particulate in the chamber air. The filters from the first test group (non-micronised) were retained and subjected to analysis to determine the amounts of Styrene/N-phenyl maleimide co-polymer in the collected dust.

Each air sample was withdrawn, at 4 litres per minute, through a weighed glass fibre filter (Whatman GF/A) mounted in an open face filter holder. The volume of the air sample was measured with a wet-type gas meter.

Two additional air samples were taken during each exposure using a Marple cascade impactor(1). The samples were taken approximately 1.5 and 3.5 hours after the start of exposure.

The material collected on the stages of the sampler was weighed to determine the particle size distribution of the particulate in the test atmosphere.

The collection characteristics for the sampler used at a sampling rate of 2 litres per minute are shown in Table 2.

The method of analysis for Styrene/N-phenyl maleimide co-polymer is described in Appendix 1.

Chamber air temperature and humidity

The air temperature in the exposure chamber was measured with a mercury-in-glass thermometer and relative humidity was measured using an ADC infra-red vapour analyser for the non-micronised sample, and a Cassella type analyser. The temperature and humidity were recorded at the start of exposure and then at 30-minute intervals during the 4-hour exposure.

(1) Model 296, Andersen Samplers Inc., Atlanta, GA, U.S.A.
(2) 11 minutes is the theoretical time required for the concentration of aerosol in the chamber to reach 90% of its final value under the conditions of exposure employed

Observations

Clinical signs

The rats were observed continuously for signs of reaction to the test substance during the exposures and at least twice daily throughout the observation periods. The clinical signs were recorded at the end of the chamber equilibration period, at 0.25, 0.5 and 1.0 hours and then at hourly intervals during the exposure. During the observation period, the clinical signs were recorded once in the morning and then as necessary following a later check for clinical signs.

Bodyweight

All rats were weighed daily from the day of delivery to the Huntingdon Research Centre until the end of the observation period.

Food and water consumption

The amount of food and water consumed by each cage of rats was measured daily from the day following arrival. The daily mean intakes of food and water for each rat were calculated from the recorded data.

Terminal studies

At the end of the 14-day observation period, the rats were anaesthetised by intraperitoneal injection of pentobarbitone sodium and killed by exsanguination.

All rats were subjected to a detailed macroscopic examination. The lungs were removed, dissected clear of surrounding tissue and weighed in order to calculate the lung weight to bodyweight ratio.

The lungs were infused with, and preserved in, buffered 10% formalin together with samples of the liver and kidneys for microscopic examination.

The fixed tissues were embedded in paraffin wax and processed routinely. Four-micron sections were prepared, stained with haemotoxylin and eosin and examined under the light microscope.

RESULTS

CHAMBER ATMOSPHERE CONDITIONS

Concentration of Styrene/N-phenyl maleimide co-polymer

The analysis results for the air samples taken during the exposures are shown in Table 1.

The mean concentrations of Styrene/N-phenyl maleimide co-polymer as received and in micronised form found in the chamber air were:

Styrene/N-phenyl maleimide co-polymer

Non-micronised			Micronised		
(mg/l)	(SD)	Nominal (mg/l)	(mg/l)	(SD)	Nominal (mg/l)
1.33	0.18	9.4	2.11	0.07	10.1

SD Standard deviation

The concentrations of Styrene/N-phenyl maleimide co-polymer were the highest attainable. There were no known procedures to further increase the concentration in air.

Particle size distribution

The results for the air samples taken for determination of the particle size distribution of Styrene/N-phenyl maleimide co-polymer are shown in Table 2 and summarised in the following table:

Non-micronised				Micronised			
MMAD (μm)	σg	% respirable (<6 μm)	% <1 μm	MMAD (μm)	σg	% respirable (<6 μm)	% <1 μm
5.1	2.84	55.8	5.8	4.0	2.84	65.2	9.2

There were no known procedures to further increase the respirable fraction or the proportion of particles in the sub-micron size range.

Chamber air temperature and relative humidity

The mean chamber air temperature, relative humidity and the standard deviation (SD) of the means for the groups were:

	Group	Temperature (°C)		Relative humidity (%)	
		Mean	SD	Mean	SD
Non-micronised	1A (Control)	25	0.5	42	5.7
	2A (Test)	24	0.0	53	3.8
Micronised	1B (Control)	24	0.4	41	5.1
	2B (Test)	24	0.5	41	2.8

There were no extremes of temperature or humidity considered likely to influence the results of the study.

CLINICAL OBSERVATIONS

Mortality

There were no deaths within 14 days following exposure to Styrene/N-phenyl maleimide co-polymer at the maximum attainable concentrations of 1.33 or 2.11 mg/l in air.

Clinical signs

(a) **During the exposure**

The incidence of clinical signs observed during exposure is shown in Table 3. The signs were not visible during the exposures due to the test atmospheres.

(b) **During the observation period**

The incidence of clinical signs seen during the observation period is shown in Table 4. Column 0 of this table shows the observations made when the rats were removed from the exposure chamber. At this time, signs evident in rats exposed to Styrene/N-phenyl maleimide co-polymer included exaggerated respiratory movements, and test material on fur and tail. The exaggerated respiratory movements were evident for 1 day following exposure to 1.33 mg/l of air and on day of exposure for rats exposed at 2.11 mg/l of air.

Residues of the test substance were visible on the tail for 1 day following exposure in rats exposed at 2.11 mg/l of air.

Recovery from the effects of exposure was complete in all rats by Day 2 of the observation period.

Bodyweight

The group mean and individual bodyweights are shown in Table 5. The group mean bodyweights are also shown in Figure 3.

There were slight decreases of bodyweight or reductions in the rate of bodyweight gain for 1 day following exposure to Styrene/N-phenyl maleimide co-polymer. Subsequently, weight gain for rats exposed to Styrene/N-phenyl maleimide co-polymer was similar to that of the control rats.

Food consumption

The food consumption data are presented in Table 6.

Food consumption was reduced for 1 day following exposure to Styrene/N-phenyl maleimide co-polymer.

Water consumption

The water consumption data are presented in Table 7.

Water consumption for rats exposed to Styrene/N-phenyl maleimide co-polymer was slightly reduced for up to 1 day in male rats exposed at 1.33 mg/l of air and also rats exposed at 2.11 mg/l of air (micronised sample).

TERMINAL STUDIES

Lung weight to bodyweight ratio

The lung weight to bodyweight ratio for individual rats is shown in Table 8.

The lung weight to bodyweight ratios for 2 female rats exposed at 1.33 mg/l of air (non-micronised) and one male rat exposed at 2.11 mg/l of air (micronised) were higher than that of the control rats.

Estimation of the LC_{50} (4-hour) for Styrene/N-phenyl maleimide co-polymer

There were no deaths following exposure at 1.33 or 2.11 mg/l of air. The LC_{50} (4-hour) for Styrene/N-phenyl maleimide co-polymer is therefore in excess of 2.11 mg/l of air.

Macroscopic pathology

The macroscopic pathological findings for individual rats are included in Appendix 2.

Dark spots were found on the lungs of 6/10 control rats and 7/10 test rats exposed at 1.33 mg/l. There were no abnormalities in rats exposed at 2.11 mg/l of air (micronised).

Microsopic pathology

The findings for individual rats are included in Appendix 2 and the incidence of findings is shown in Table 9. The following comments are made in summary:

Non-micronised sample of Styrene/N-phenyl maleimide co-polymer.

The following treatment-related changes were observed:

An apparent increase in the incidence of minimal pneumonitis, minimal increased numbers of alveolar macrophages and minimal perivascular lymphoid infiltration in lungs of the female rats of the 1.33 mg/l test group compared to the controls.

All the other microscopic changes were considered of no toxicological importance.

Micronised sample of Styrene/N-phenyl maleimide co-polymer

Treatment-related changes:

Lungs

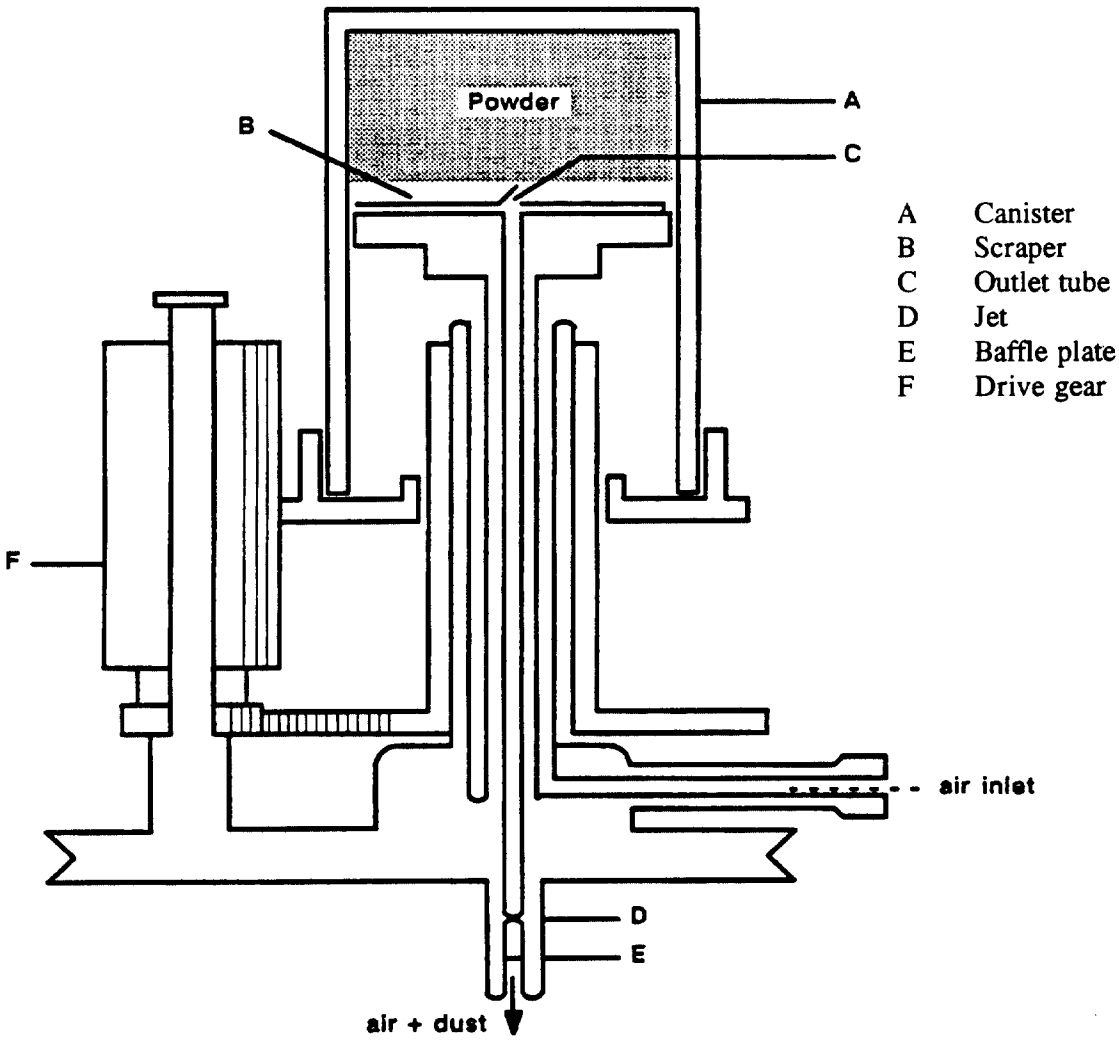
Alveolar macrophages containing globular inclusions were detected in 9/10 rats from the treated group. In one of these male rats, these macrophages were aggregates around terminal bronchioles.

Incidental findings:

All other lesions detected in the lungs examined were considered spontaneous in origin and therefore of no toxicological significance.

FIGURE 1

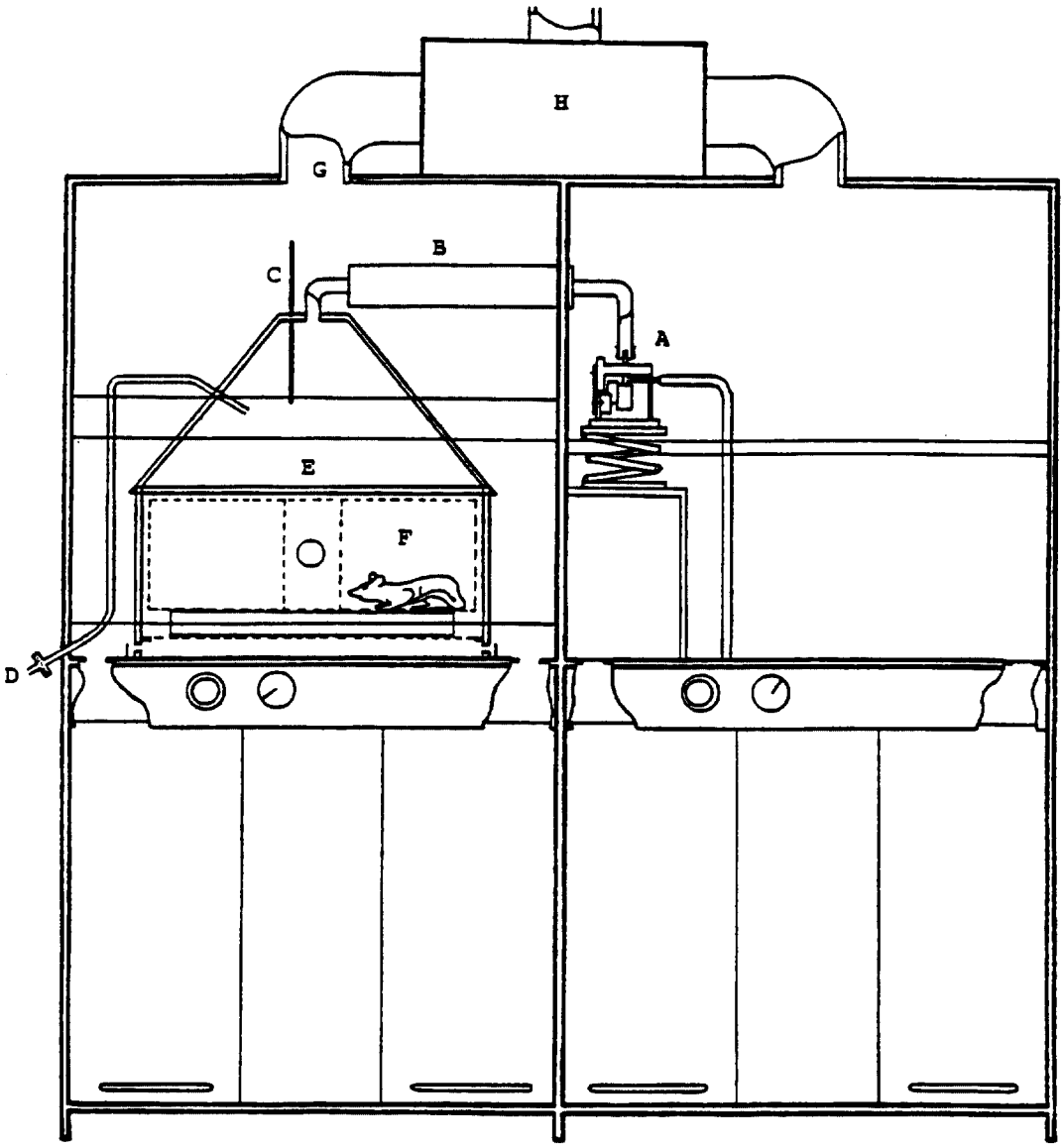
Wright dust generator



A Canister
B Scraper
C Outlet tube
D Jet
E Baffle plate
F Drive gear

FIGURE 2

Exposure system



A	Wright Dust Feed Mechanism	E	Exposure chamber
B	Aerosol neutraliser	F	Holding cage
C	Thermometer	G	Extract from outer chamber
D	Sample line to water vapour analyser	H	Filter/Extract unit

FIGURE 3a

Group mean bodyweights - males

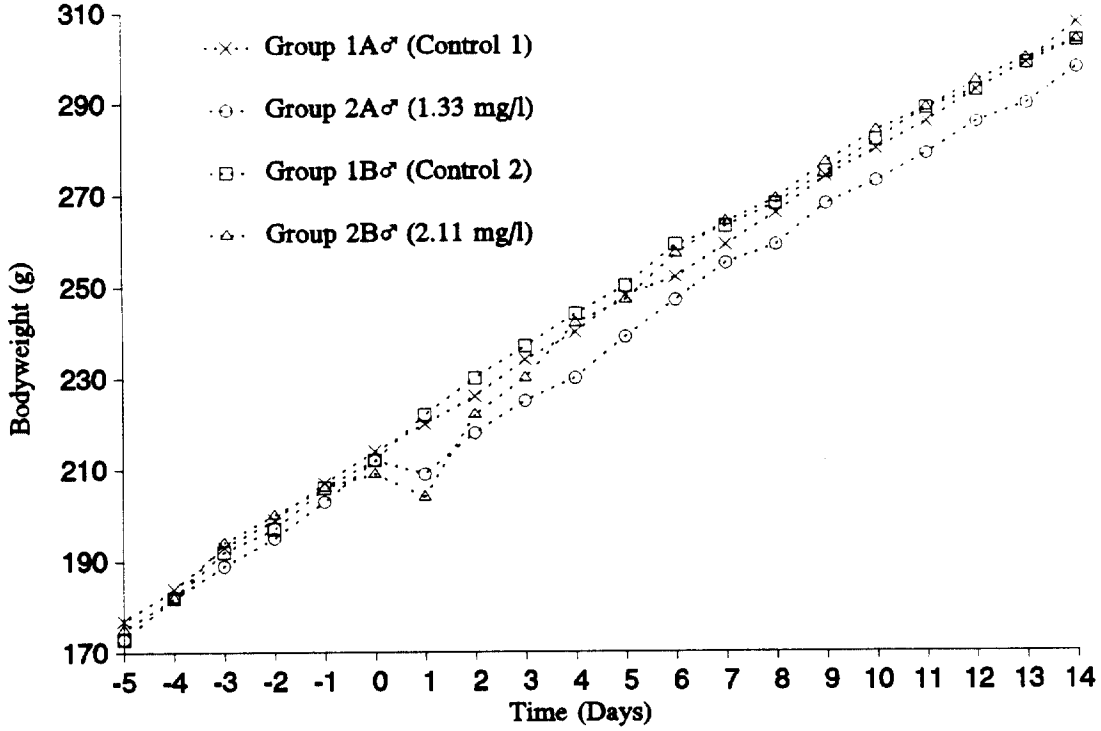


FIGURE 3b

Group mean bodyweights - females

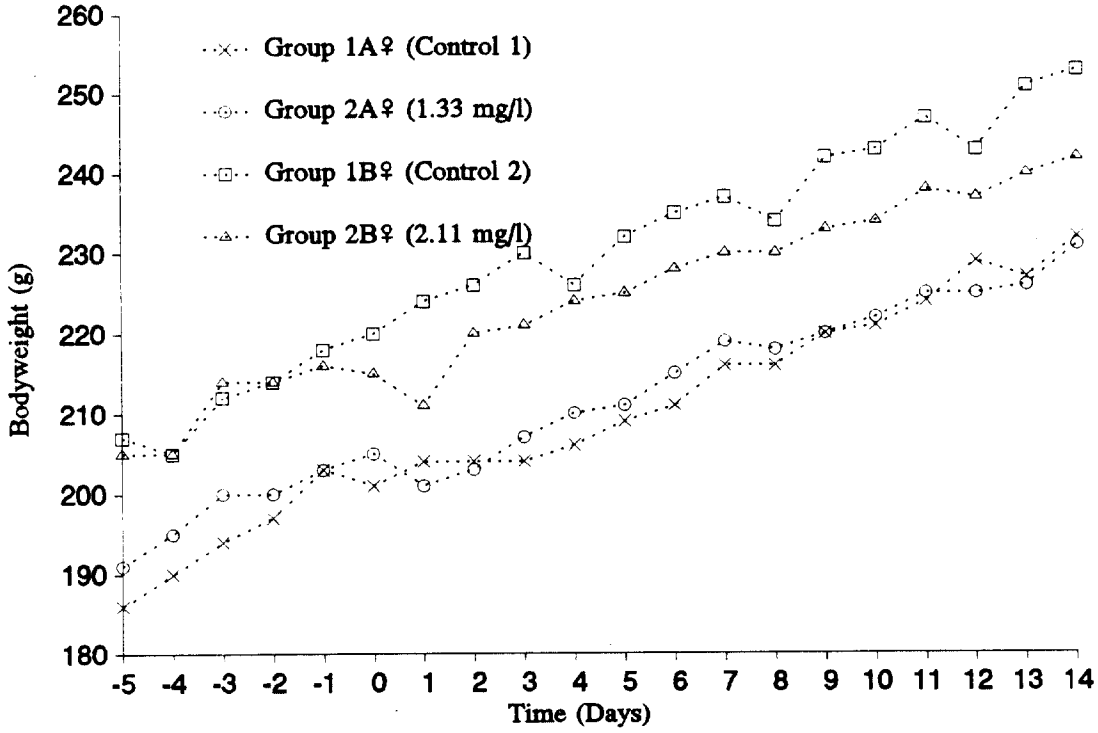


TABLE 1

Concentrations of Styrene/N-phenyl maleimide co-polymer

Non-micronised sample - Analytical results

Group	Sample	Time	Amount in air (mg/l)	Nominal (mg/l) (1)
2A	2.1	0h : 30m	1.55	
	2.2	1h : 00m	1.41	
	2.3	2h : 00m	1.39	
	2.4	3h : 00m	1.11	
	2.5	3h : 50m	1.17	
		Mean	1.33	
		SD	0.18	9.4

Micronised (air milled) sample - Gravimetric results

Group	Sample	Time	Amount in air (mg/l)	Nominal (mg/l) (1)
2B	2.1	0h : 30m	2.01	
	2.2	1h : 00m	2.19	
	2.3	2h : 00m	2.10	
	2.4	3h : 00m	2.13	
	2.5	3h : 50m	2.10	
		Mean	2.11	
		SD	0.07	10.1

(1) Calculated from the weight of test substance dispersed and the total volume of air supplied to the exposure system

SD Standard deviation

TABLE 2

Particle size distribution of Styrene/N-phenyl maleimide co-polymer

(a) **Gravimetric results (non-micronised)**

Group	Sample	Time taken	Stage	Cut-off size (μm)	Amount collected (μg)
2A	PSD 1	1h : 30m	3	9.8	0.32
			4	6.0	1.11
			5	3.5	0.85
			6	1.55	0.25
			7	0.93	0.03
			8	0.52	0.07
			Filter	0.0	0.05
				Totals	2.68
	PSD 2	3h : 30m	3	9.8	0.23
			4	6.0	0.88
			5	3.5	0.67
			6	1.55	0.25
			7	0.93	0.07
			8	0.52	0.06
			Filter	0.0	0.11
				Totals	2.27

(b) **Calculations for non-micronised**

Cut-off size (μm)	% less than size (cumulative)
9.8	88.8
6.0	48.6
3.5	17.9
1.55	7.8
0.93	5.8
0.52	3.2
MMAD	5.1 μm
σg	2.84
25% size	2.5 μm
% <1 μm	5.8
% respirable	55.8

MMAD Mass median aerodynamic diameter

σg Standard geometric deviation

TABLE 2

(Particle size distribution - continued)

(c) **Gravimetric results (micronised)**

Group	Sample	Time taken	Stage	Cut-off size (μm)	Amount collected (μg)
2B	PSD 1	1h : 30m	3	9.8	0.13
			4	6.0	0.62
			5	3.5	0.63
			6	1.55	0.22
			7	0.93	0.08
			8	0.52	0.12
			Filter	0.0	0.17
				Totals	1.97
	PSD 2	3h : 30m	3	9.8	0.13
			4	6.0	0.80
			5	3.5	0.51
			6	1.55	0.29
			7	0.93	0.05
			8	0.52	0.02
			Filter	0.0	0.03
				Totals	1.83

(d) **Calculations for micronised**

Cut-off size (μm)	% less than size (cumulative)
9.8	93.2
6.0	55.8
3.5	25.8
1.55	12.4
0.93	9.0
0.52	5.3
MMAD	4.0 μm
σg	2.84
25% size	2.0 μm
% <1 μm	9.2
% respirable	65.2

MMAD Mass median aerodynamic diameter
σg Standard geometric deviation

TABLE 3

Clinical signs during exposure

Non-micronised

Group	Signs	Number showing signs						
		Time in hours						
		0*	0.25	0.5	1.0	2.0	3.0	4.0
1A♂ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5
1A♀ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5
2A♂ (1.33 mg/l)	Test material on fur	5						
	Animals not visible due to test atmosphere	5	5	5	5	5	5	5
2A♀ (1.33 mg/l)	Test material on fur	5						
	Animals not visible due to test atmosphere	5	5	5	5	5	5	5

Micronised

Group	Signs	Number showing signs						
		Time in hours						
		0*	0.25	0.5	1.0	2.0	3.0	4.0
1B♂ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5
1B♀ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5
2B♂ (2.11 mg/l)	Animals not visible due to test atmosphere	5	5	5	5	5	5	5
2B♀ (2.11 mg/l)	Animals not visible due to test atmosphere	5	5	5	5	5	5	5

* Clinical signs recorded during the 11-minute equilibration period

TABLE 4

Clinical signs during observation period

Non-micronised

Group	Signs	Number showing signs														
		Day of observation period														
		0*	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1A♂ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1A♀ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2A♂ (1.33 mg/l)	Normal appearance and behaviour			5	5	5	5	5	5	5	5	5	5	5	5	5
	White test material on fur	5														
	Exaggerated respiratory movements	5	5													
2A♀ (1.33 mg/l)	Normal appearance and behaviour			5	5	5	5	5	5	5	5	5	5	5	5	5
	White test material on fur	5														
	Exaggerated respiratory movements	5	5													

* Clinical signs recorded after exposure on the day of exposure

TABLE 4

(Clinical signs - continued)

Micronised

Group	Signs	Number showing signs														
		Day of observation period														
		0*	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1B♂ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1B♀ (Control)	Normal appearance and behaviour	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2B♂ (2.11 mg/l)	Normal appearance and behaviour			5	5	5	5	5	5	5	5	5	5	5	5	5
	White test material on fur and tail	5														
	Test material on tail only		5													
	Exaggerated respiratory movements	5														
2B♀ (2.11 mg/l)	Normal appearance and behaviour			5	5	5	5	5	5	5	5	5	5	5	5	5
	White test material on fur and tail	5														
	Test material on tail only		5													
	Exaggerated respiratory movements	5														

* Clinical signs recorded after exposure on the day of exposure

TABLE 5

Individual and group mean bodyweights (g)

Non-micronised

Group	Rat	Pre-exposure					Day of observation														
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1A♂ (Control)	151	176	186	195	199	209	209	217	218	227	233	239	247	256	261	267	272	280	289	290	301
	152	180	188	195	203	210	221	228	233	240	250	258	266	269	284	291	300	306	314	323	329
	72R	169	175	184	191	199	208	211	221	229	236	246	253	260	260	268	273	279	284	289	296
	154	188	196	206	213	220	229	234	241	252	259	263	251	260	281	285	293	297	305	309	318
	155	171	177	185	191	197	205	211	215	222	228	233	244	251	253	260	263	268	275	283	295
	Mean	177	184	193	199	207	214	220	226	234	241	248	252	259	268	274	280	286	293	299	308
1A♀ (Control)	156	190	196	199	198	205	209	211	206	206	216	217	214	220	227	231	225	235	241	239	245
	157	191	192	200	203	210	200	205	208	207	205	212	215	216	216	224	226	226	230	229	232
	158	181	185	190	194	200	197	200	203	209	205	211	215	219	219	226	227	227	230	236	240
	159	185	189	188	195	199	196	200	199	200	201	196	201	208	203	203	210	214	219	208	215
	160	185	190	192	195	201	201	206	202	200	205	207	210	215	216	214	217	220	223	221	227
	Mean	186	190	194	197	203	201	204	204	204	206	209	211	216	216	220	221	224	229	227	232
2A♂ (1.33 mg/l)	161	161	169	176	182	190	198	190	195	203	210	217	226	235	240	246	252	258	262	268	275
	162	179	187	195	200	208	217	217	229	236	242	252	262	270	280	290	301	305	315	319	326
	163	176	186	192	199	209	217	217	224	232	231	246	248	255	262	271	273	285	292	298	306
	164	171	182	188	192	201	212	209	219	225	233	239	247	255	258	267	271	276	280	284	292
	165	178	187	195	201	209	217	212	222	228	235	241	250	260	257	264	270	273	282	282	290
	Mean	173	182	189	195	203	212	209	218	225	230	239	247	255	259	268	273	279	286	290	298
2A♀ (1.33 mg/l)	166	192	197	196	200	205	208	202	206	212	214	210	218	217	226	221	222	231	233	229	232
	167	190	197	205	204	206	210	210	210	208	215	218	222	225	227	232	231	232	238	240	245
	168	192	196	205	207	210	206	207	209	214	209	216	220	225	221	227	229	232	225	234	240
	169	192	193	192	187	193	198	190	188	194	195	199	205	211	202	204	210	205	207	205	211
	170	188	191	202	200	202	205	197	202	205	216	210	212	218	216	214	216	225	224	223	227
	Mean	191	195	200	200	203	205	201	203	207	210	211	215	219	218	220	222	225	225	226	231

0 Day of exposure
R Replacement rat. Original rat (153♂) replaced because of low weight gain

TABLE 5

(Individual and group mean bodyweights - continued)

Micronised

Group	Rat	Pre-exposure					Day of observation														
		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1B♂ (Control)	21	177	189	200	206	211	228	234	243	251	258	267	275	286	291	302	308	316	322	331	336
	22	169	178	189	190	195	201	210	219	228	237	246	253	259	260	268	281	287	292	298	303
	23	162	169	178	182	192	196	207	213	218	225	228	236	242	248	253	259	266	271	275	277
	24	179	190	201	208	218	220	231	240	249	256	262	280	271	278	286	287	295	298	306	308
	25	178	186	194	201	212	215	226	234	240	244	247	251	256	264	266	276	279	282	284	294
	Mean	173	182	192	197	206	212	222	230	237	244	250	259	263	268	275	282	289	293	299	304
1B♀ (Control)	26	212	204	218	218	224	226	230	233	238	224	239	243	244	237	248	255	254	243	255	260
	27	198	201	207	209	213	222	219	225	218	224	228	230	228	230	236	236	237	241	246	249
	28	204	208	212	212	217	220	222	213	225	224	224	223	231	231	232	229	238	238	238	231
	29	205	199	207	214	219	214	226	226	231	227	237	239	243	237	252	251	253	244	260	263
	30	214	212	216	217	216	218	225	232	237	229	234	242	238	237	244	246	253	249	258	260
	Mean	207	205	212	214	218	220	224	226	230	226	232	235	237	234	242	243	247	243	251	253
2B♂ (2.11 mg/l)	31	174	184	193	203	205	202	191	212	221	233	238	246	254	262	264	274	278	282	289	290
	32	175	180	191	195	206	211	205	220	227	241	245	253	259	264	272	281	286	287	297	301
	33	177	184	198	202	208	208	211	227	236	247	252	266	272	281	291	296	301	312	320	318
	682R	169	176	190	197	201	211	198	221	229	240	248	256	267	269	281	290	296	304	310	317
	35	180	187	198	203	210	212	213	228	235	249	253	263	268	270	275	281	284	290	294	296
	Mean	175	182	194	200	206	209	204	222	230	242	247	257	264	269	277	284	289	295	302	304
2B♀ (2.11 mg/l)	36	201	205	204	208	209	209	203	215	215	218	216	223	225	224	220	225	231	231	227	233
	37	191	192	202	199	202	204	196	205	203	204	208	212	210	213	215	217	217	215	221	221
	38	205	198	211	212	218	213	203	214	217	221	220	224	225	223	224	225	226	230	230	233
	39	212	210	221	223	223	215	223	232	232	234	238	239	240	233	247	247	250	244	254	258
	40	214	222	232	225	230	235	228	235	237	241	244	244	251	259	260	257	266	266	270	266
	Mean	205	205	214	213	216	215	211	220	221	224	225	228	230	230	233	234	238	237	240	242

0 Day of exposure
R Replacement rat. Original rat (34♂) replaced because of high weight gain

TABLE 6

Group mean daily food consumption (g/rat)

Non-micronised

Group	Days																		
	Pre-exposure					Post exposure													
	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1A♂ (Control)	21	22	22	22	21	22	27	28	26	28	28	28	27	27	27	28	27	31	26
2A♂ (Test)	23	22	21	23	24	15	25	25	24	25	26	25	26	26	27	26	27	27	26
1A♀ (Control)	20	20	19	20	17	18	21	20	19	20	20	22	20	20	20	21	19	22	21
2A♀ (Test)	20	20	17	18	18	13	20	19	16	20	19	21	19	19	21	21	20	20	20

Micronised

Group	Days																		
	Pre-exposure					Post exposure													
	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1B♂ (Control)	27	27	25	28	25	27	29	29	28	30	30	30	30	31	32	31	30	30	30
2B♂ (Test)	26	28	27	26	21	11	29	30	31	31	32	32	32	32	32	33	30	30	30
1B♀ (Control)	23	23	25	23	21	23	24	24	21	27	25	26	22	28	27	28	22	25	23
2B♀ (Test)	25	26	24	24	21	12	23	23	23	24	24	25	23	24	24	27	22	22	22

TABLE 7

Group mean daily water consumption (g/rat)

Non-micronised

Group	Days																	
	Pre-exposure					Post exposure												
	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1A♂ (Control)	23	24	23	23	24	25	27	29	27	26	28	26	28	27	27	28	28	30	27
2A♂ (Test)	23	23	22	23	23	20	26	25	25	24	24	25	26	25	26	26	26	25	25
1A♀ (Control)	20	23	21	22	20	19	22	25	23	25	25	28	32	34	32	34	37	38	36
2A♀ (Test)	25	25	22	21	23	21	26	26	24	27	25	27	28	29	30	25	37	51	28

Micronised

Group	Days																	
	Pre-exposure					Post exposure												
	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1B♂ (Control)	30	30	29	28	28	32	31	33	33	34	31	33	33	34	34	32	33	34	34
2B♂ (Test)	31	33	32	30	25	20	39	34	37	35	36	36	34	35	36	34	34	33	33
1B♀ (Control)	28	31	32	31	26	31	30	31	26	35	33	32	26	35	36	34	23	32	30
2B♀ (Test)	30	29	28	26	22	23	30	27	27	29	28	29	25	29	29	30	26	27	27

TABLE 8

Lung weight to bodyweight ratios

Non-micronised

Group	Rat no.	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW x 100/BW)
1A♂ (Control)	151	1.28	301	0.43
	152	1.49	329	0.45
	72R	1.53	296	0.52
	154	1.36	318	0.43
	155	1.59	295	0.54
			Mean	0.47
			SD	0.052
1A♀ (Control)	156	1.18	245	0.48
	157	1.27	232	0.55
	158	1.31	240	0.55
	159	1.17	215	0.54
	160	1.30	227	0.57
			Mean	0.54
			SD	0.034
2A♂ (Test)	161	1.29	275	0.47
	162	1.56	326	0.48
	163	1.55	306	0.51
	164	1.50	292	0.51
	165	1.45	290	0.50
			Mean	0.49
			SD	0.018
2A♀ (Test)	166	1.14	232	0.49
	167	1.52	245	0.62
	168	1.45	240	0.60
	169	1.13	211	0.54
	170	1.26	227	0.56
			Mean	0.56
			SD	0.051

SD Standard deviation
R Replacement rat

TABLE 8

(Lung weight to bodyweight ratios - continued)

Micronised

Group	Rat no.	Lung weight (g)	Bodyweight (g)	Lung to bodyweight ratio (LW x 100/BW)
1B♂ (Control)	21	1.54	336	0.46
	22	1.49	303	0.49
	23	1.32	277	0.48
	24	1.59	308	0.52
	25	1.56	294	0.53
			Mean	0.50
			SD	0.029
1B♀ (Control)	26	1.38	260	0.53
	27	1.32	249	0.53
	28	1.17	231	0.51
	29	1.65	263	0.63
	30	1.50	260	0.58
			Mean	0.56
			SD	0.049
2B♂ (Test)	31	1.78	290	0.61
	32	1.51	301	0.50
	33	1.59	318	0.50
	682R	1.56	317	0.49
	35	1.52	296	0.51
			Mean	0.52
			SD	0.050
2B♀ (Test)	36	1.36	233	0.58
	37	1.29	221	0.58
	38	1.37	233	0.59
	39	1.39	258	0.54
	40	1.38	266	0.52
			Mean	0.56
			SD	0.030

SD Standard deviation
R Replacement rat

TABLE 9

Microscopic pathology incidence summary

Non-micronised test substance

	Group 1	Group 2	Group 1	Group 2
	--- Males ---		-- Females --	
Animals on study	5	5	5	5
Animals completed	5	5	5	5
Lungs				
Examined	5	5	5	5
No abnormalities detected	1	2	3	0
Pneumonitis (Total)	2	2	2	4
Minimal	2	2	2	4
Perivascular lymphoid infiltration (Total)	0	2	1	5
Minimal	0	2	1	5
Increased numbers of alveolar macrophages(Total)	0	0	0	3
Minimal	0	0	0	3
Vascular congestion	2	2	1	1
Fibrous thickening of alveolar septa	1	0	0	0

Micronised test substance

	Group 1	Group 2	Group 1	Group 2
	--- Males ---		-- Females --	
Animals on study	5	5	5	5
Animals completed	5	5	5	5
Lungs				
Examined	5	5	5	5
No abnormalities detected	1	0	2	0
Macrophages containing globular inclusions(Total)	0	5	0	4
Minimal	0	5	0	4
Macrophage aggregates around terminal bronchioles(Total)	0	1	0	0
Minimal	0	1	0	0
Macrophages with interstitial alveolar wall thickening(Total)	2	0	1	0
Minimal	2	0	1	0
Alveolitis (Total)	2	0	0	0
Minimal	2	0	0	0
Recent alveolar haemorrhage (Total)	0	0	1	0
Minimal	0	0	1	0
Macrophage aggregations (Total)	0	0	1	0
Minimal	0	0	1	0
Peribronchiolar fibrosis (Total)	0	1	0	1
Minimal	0	1	0	1
Bronchiolar epithelial hypertrophy (Total)	0	0	0	1
Minimal	0	0	0	1

APPENDICES

APPENDIX 1

Methods of analysis

Method of analysis for Styrene/N-phenyl maleimide co-polymer

1. **Instrumentation and apparatus**

HPLC:	Shimadzu SIL-6A autosampler. Shimadzu SCL-6A system controller. Shimadzu LC-6A pump. Shimadzu C-R4A integrator. Spectra-Physics LC 871 detector.
Apparatus:	Volumetric flasks and pipettes. Extraction columns, 7 mm i.d. Sample vials.

2. **Reagents**

Tetrahydrofuran:	'HPLC' grade Fisons.
Styrene/N-phenyl maleimide co-polymer:	Supplied by Sponsor.

3. **Preparation of sample solutions for Styrene/N-phenyl maleimide co-polymer**

The filters from the open face sampler were transfered to extraction columns and compacted with a glass rod. The Styrene/N-phenyl maleimide co-polymer was eluted with five 2 ml potions of tetrahydrofuran into a 20 ml volumetric flask and diluted to volume with tetrahydrofuran.

The solutions were diluted with tetrahydrofuran to obtain solutions for analysis with expected maximum concentrations of Styrene/N-phenyl maleimide co-polymer of less than 50 μg/ml.

APPENDIX 1

(Method of analysis - continued)

4. **HPLC operating conditions**

4.1.	Column:	TSK-GEL G1000HXL 300 x 7.8 mm i.k. (H10XE0011).
	Mobile phase:	Tetrahydrofuran.
	Flow rate:	0.5 ml/min.
	Injection volume:	20 μl (nominal fixed loop).
	Detector range:	0.16 AUFS.
	Detector wavelength:	220 nm.
	Retention time:	Typically 8.6 minutes.

4.2. **Analysis of samples**

A 20 μl aliquot of of each sample solution was injected onto the HPLC column using the autosampler. The concentration of Styrene/N-phenyl maleimide co-polymer was evaluated from the standard curve calculated below:

$$Cx = \frac{(Ax - I)}{S}$$

Where Cx =concentration of Styrene/N-phenyl maleimide co-polymer (μg/ml)
Ax =peak area due to Styrene/N-phenyl maleimide co-polymer
S =gradient of standard curve
I =intercept of standard curve

APPENDIX 1

(Method of analysis - continued)

4.3. **Standardisation**

Approximately 100 mg of Styrene/N-phenyl maleimide co-polymer was accurately weighed into a 100 ml volumetric flask, dissolved in tetrahydrofuran and diluted to volume with tetrahydrofuran. The solution was diluted with tetrahydrofuran to obtain standard solutions containing Styrene/N-phenyl maleimide co-polymer at nominal concentrations within the range 5.0 μg/ml and 50 μg/ml. Aliquots of the standard solutions were injected and the mean areas for Styrene/N-phenyl maleimide co-polymer were calculated for each standard solution. A standard curve was calculated for Styrene/N-phenyl maleimide co-polymer from the mean areas by regression analysis.

APPENDIX 2

Pathological data relating to individual rats

	Non-micronised		Micronised	
Group:	1A	2A	1B	2B
Compound:	-	Styrene/N-phenyl maleimide co-polymer		
Level	Control	1.33	Control	2.11

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 151♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Dark spots on all lobes.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 152♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Area)
Vascular congestion

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 72♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 154♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Fibrous thickening of alveolar septa: (Focal)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 155♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Small dark spots on all lobes.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Vascular congestion

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 156♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Small dark spots on all lobes.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 157♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Right anterior lobe, dark line.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 158♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Raised areas on all lobes. Right anterior lobe, dark line.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Area)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 159♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 160♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Right anterior and posterior lobes, dark spots.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focus)
Perivascular lymphoid infiltration: (Minimal , Focal)
Vascular congestion

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 161♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Small dark spots on all lobes.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Vascular congestion

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 162♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 163♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Areas of congestion all lobes.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 164♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Right anterior lobe, dark spots.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Area)
Perivascular lymphoid infiltration: (Minimal , Focal)
Vascular congestion

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 165♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Small dark spots on all lobes.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)
Perivascular lymphoid infiltration: (Minimal)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 166♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Right posterior lobe, dark spot.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Perivascular lymphoid infiltration: (Minimal , Focal)
Increased numbers of alveolar macrophages: (Minimal)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 167♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Appear mottled.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)
Perivascular lymphoid infiltration: (Minimal , Foci)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 168♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)
Perivascular lymphoid infiltration: (Minimal , Focal)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 169♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)
Perivascular lymphoid infiltration: (Minimal , Foci)
Increased numbers of alveolar macrophages: (Minimal)

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 1.33 mg/l

Rat No/Sex: 170♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Appear mottled.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Pneumonitis: (Minimal , Focal)
Perivascular lymphoid infiltration: (Minimal , Focal)
Increased numbers of alveolar macrophages: (Minimal , Focal)
Vascular congestion

Pathologist: H.Singh

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 21♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 22♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages with interstitial alveolar wall thickening: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 23♂ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Right posterior lobe, dark subpleural foci.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Alveolitis: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 24♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Alveolitis: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 25♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages with interstitial alveolar wall thickening: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 26♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages with interstitial alveolar wall thickening: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 27♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 28♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following tissues were considered normal:

Lungs

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 29♀ (Terminal)

MACROSCOPIC FINDINGS

Lungs
Right posterior lobe and right middle lobe, dark subpleural foci.

All the other organs and tissues appeared normal.

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Recent alveolar haemorrhage: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: Control

Rat No/Sex: 30♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophage aggregations: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 31♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)
Macrophage aggregates around terminal bronchioles: (Minimal)
Peribronchiolar fibrosis: (Minimal , Area)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 32♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 33♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 682♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 35♂ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 36♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 37♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)
Bronchiolar epithelial hypertrophy: (Minimal , Focus)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 38♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 39♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Peribronchiolar fibrosis: (Minimal)

Pathologist: D.J.Lewis

APPENDIX 2

(Pathology - continued)

Compound: Co-polymer

Dosage Level: 2.11 mg/l

Rat No/Sex: 40♀ (Terminal)

MACROSCOPIC FINDINGS

No abnormalities detected

MICROSCOPIC FINDINGS

The following observations were noted:

Lungs
Macrophages containing globular inclusions: (Minimal)

Pathologist: D.J.Lewis

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C 20460

Hidetakta Yatagai, Ph.D.
General Manager
NA Industries, Inc.
New York Office (Nippon Shokubai)
101 East 52nd Street
New York, New York 10022

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 1 2 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000 Initial) assigned by EPA to your submission(s). Please cite this number when submitting follow-up or supplemental information and refer to the enclosure on the reverse side "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12720 A

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0993-12720 SEQ A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: NA Industries, Inc.

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 09/27/93 OTS DATE: 10/01/93 CSRAD DATE: 10/29/93

CHEMICAL NAME: CAS#:

Styrene/N-phenyl maleimide co-polymer, non-micronised — Unknown — [redacted] — 541-59-3

[redacted] — 100-42-5

Styrene/N-phenyl maleimide co-polymer, micronised — Unknown

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	(0243)	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	0248	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	0224	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
(0212)	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES (CONTINUE))	YES (DROP/REFER)	RAT	(LOW) Acute inhalation toxicity		
	NO (DROP)	NO (CONTINUE)		MED		
	(DETERMINE)	REFER:		HIGH		

COMMENTS: Non-Cap

8(e)-12720A
LOW--Acute inhalation toxicity

Acute inhalation toxicity. Rats (10/dose) were exposed to an aerosol of 1.33 (non micronised) and 2.11 (micronised) mg/l (g/m3) for 4 hours. There were no deaths. Exaggerated breathing and increased incidence of mild pneumonitis, number of alveolar macrophages containing globular inclusions, and perivascular lymphoid infiltration of the lungs were reported.